Retinal Arteriolar Caliber Predicts Incident Retinopathy

The Australian Diabetes, Obesity and Lifestyle (AusDiab) Study

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Changes in retinal vascular caliber may reflect subclinical microvascular disease and provide prognostic information regarding risk of retinopathy. In this study, we examined the prospective association of retinal vascular caliber with retinopathy risk in an Australian population-based cohort. A total of 906 participants without retinopathy at baseline had retinal vascular caliber measured from photographs and were followed-up for 5 years for incident retinopathy. After adjusting for age, sex, systolic blood pressure, A1C, and other risk factors, individuals with wider retinal arteriolar caliber (widest 25% vs. the remaining three-quarters of the population) were more likely to develop incident retinopathy (odds ratio 4.79 [95% CI 1.57–14.58]). This association was not significant in individuals without diabetes. Venular caliber did not predict incident retinopathy. Our findings suggest that retinal arteriolar dilatation is a specific sign of diabetic microvascular dysfunction and may be a preclinical marker of diabetic retinopathy.

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Emerging evidence suggests that quantitative assessment of retinal vascular caliber may provide prognostic information regarding the risk of diabetic microvascular complications such as retinopathy (1–4). Wider retinal arterioles have been shown to predict the incidence (1) and progression (2) of diabetic retinopathy, in keeping with experimental work that indicates a role for retinal arteriolar dilatation in the pathogenesis of diabetic retinopathy (5). According to the laws of Starling and Laplace, retinal arteriolar dilatation causes a rise in capillary pressure, which in turn can lead to capillary wall dilatation (microaneurysm), leakage (edema), and rupture (hemorrhage), all classical signs of diabetic retinopathy (6–8).

However, not all studies have reported an association of retinal arteriolar dilatation with risk of retinopathy (4). Reasons for these inconsistencies are not apparent but could be related to imprecise diagnoses of diabetes (i.e., those not based on an oral glucose tolerance test). Additional studies are clearly needed. Our study examines the relationship of retinal vascular caliber and 5-year incident retinopathy in the Australian Diabetes, Obesity and Lifestyle (AusDiab) Study.

RESEARCH DESIGN AND METHODS

— Detailed methodology for the AusDiab Study has previously been described (9–14). Diabetes was defined based on oral glucose tolerance tests using World Health Organization recommendations. Of the original cohort (n = 2,476), 906 participants were included in the current analyses (see the online appendix available at http://dx.doi.org/10.2337/dc07-1622). At baseline and 5-year follow-up visits, two retinal photographs were taken of both eyes using a nonmydriatic digital fundus camera—one centered on the optic disc and the other on the macula (9–11)—and both photographs were viewed on color monitors. A single trained grader, masked to participants' characteristics, graded all photographs according to the simplified version of the Wisconsin grading system (15). Incident retinopathy was defined as the presence of retinal microaneurysm(s) and/or hemorrhage(s) at the 5-year examination. All retinopathy cases were adjudicated by a retinal specialist. Retinal vascular caliber was measured from baseline photographs of the left eye by trained graders according to a standardized protocol (16–19) (see the online appendix).

Logistic regression was used to determine the odds of retinopathy in individuals with wider retinal arteriolar or venular caliber, defined as widest quartile versus remaining three-quarters, with adjustment for age, sex, BMI, systolic blood pressure, A1C, and cholesterol. Both arteriolar and venular calibers were modeled simultaneously (20). Stratified analysis by diabetes status was also performed. All analyses were performed using Intercooled Stata version 9.0 (StataCorp, College Station, TX).

RESULTS

— Of the 906 participants, 250 (27.7%) had diabetes (7 with type 1) and 455 (50.4%) had impaired fasting glucose or impaired glucose tolerance. After 5 years of follow-up, 27 (3.0%) participants had developed retinopathy: 20 (8.0%) in the diabetic group, 3 (0.7%) in the impaired fasting glucose/impaired glucose tolerance group, and 4 (2.0%) with normal glucose levels.

Table 1 shows that after adjusting for age, sex, venular caliber, BMI, systolic blood pressure, A1C, and cholesterol, wider retinal arteriolar caliber was associated with 5-year incident retinopathy (odds ratio [OR] 4.79). This association was only significant in individuals with diabetes (OR 2.68 in nondiabetic participants [95% CI 0.38–18.96]). In supplementary analysis after excluding

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Table 1—*Association between retinal vascular caliber and 5-year incident retinopathy in the Australian Diabetes, Obesity and Lifestyle (AusDiab) Study*

	n	Incidence (%)	Age- and sex-adjusted OR (95% CI)	*P*	Multivariable-adjusted OR (95% CI)*	*P*
Retinal arteriolar caliber						
All participants						
Narrower 75% (<191.0 μm)	679	2.7	1.0	—	1.0	—
Widest 25% (≥191.0 μm)	227	4.0	3.62 (1.42–9.25)	0.007	4.79 (1.57–14.58)	0.006
Participants with diabetes						
Narrower 75% (<189.0 μm)	187	7.0	1.0		1.0	
Widest 25% (≥189.0 μm)	63	11.1	3.52 (1.12–10.99)	0.031	5.21 (1.24–21.88)	0.024
Retinal venular caliber						
All participants						
Narrower 75% (<220.9 μm)	679	3.4	1.0	—	1.0	—
Widest 25% (≥220.9 μm)	227	1.8	0.68 (0.22–2.12)	0.501	0.77 (0.23–2.60)	0.670
Participants with diabetes						
Narrower 75% (<219.0 μm)	187	9.1	1.0		1.0	
Widest 25% (≥219.0 μm)	63	4.8	0.59 (0.15–2.28)	0.442	0.47 (0.09–2.40)	0.364

*Adjusted for age, sex, systolic blood pressure, A1C, total cholesterol, and BMI. Models for arteriolar caliber were adjusted for venular caliber and vice versa.

participants with type 1 diabetes (n = 7), the direction of association was similar but not statistically significant (multivariable-adjusted OR 3.41 [95% CI 0.69–16.80]). Wider retinal venular caliber was not associated with incident retinopathy.

CONCLUSIONS — Our study shows that wider retinal arteriolar caliber predicts an excess risk of retinopathy independent of blood pressure, glycemic control, and other retinopathy risk factors. This association was significant among subjects with type 1 diabetes but attenuated in subjects with type 2 diabetes. The attenuation in this association could suggest either a reduced study power or a stronger association in subjects with type 1 than with type 2 diabetes. We did not observe associations between venular caliber and incident retinopathy in this sample.

Our findings are supported by other studies. A case-control study in children and adolescents with type 1 diabetes reported an association of wider retinal arterioles with incident retinopathy (1). Wider retinal arterioles were also associated with 4-year progression of retinopathy in younger-onset diabetes in the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR), although the positive association with incident retinopathy was not statistically significant (2). More recent WESDR data from older adults with type 2 diabetes also demonstrated an association of wider retinal arterioles with incident retinopathy (4,7). The lack of association seen in individuals without diabetes in our study may suggest that retinal arteriolar dilatation is a specific indicator of diabetic microvascular damage and is not a preclinical marker of nondiabetic retinopathy.

Our study provides further support for the hypothesis that retinal arteriolar dilatation plays an important role in the pathogenesis of developing retinopathy in individuals with diabetes. Experimental studies indicate that an increase in retinal blood flow and associated arteriolar dilatation are frequent in retinas of individuals with diabetes and may reflect underlying arteriolar autoregulation dysfunction (5). This could be due to hyperglycemia-mediated endothelin-1 resistance and calcium-influx channel inhibition in smooth muscle cells. These processes could impair retinal arteriolar constriction and could also augment retinal arteriolar dilatory response by reducing oxygen tension from retinal capillary nonperfusion (5). Conversely, retinal venular dilatation may represent a later sign of diabetic retinopathy. This would explain why there is some evidence of association of retinal venular dilatation with progression of retinopathy (2) but no evidence of a consistent relationship with the development of early-onset retinopathy(1,4).

Strengths of our study include its prospective design, population-based sample, and use of validated methods in measuring retinal vascular caliber. Potential limitations include selection bias due to the large proportion of excluded cases. Because retinopathy was not ascertained from seven-field retinal photographs, there may also be an underestimation of both retinopathy prevalence and incidence. Finally, the number of individuals with incident diabetic retinopathy was relatively small in this sample, limiting the power and precision of our risk estimates.

In summary, we show that retinal arteriolar dilatation measured from retinal photographs may be a preclinical marker of early diabetic retinopathy. Further research in and development of retinal image analysis may offer the potential for this technique to improve risk stratification of this blinding condition in individuals with diabetes.

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